The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 8, 2025

HORMONAL FLUCTUATIONS AND MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME IN WOMEN: THE ROLE OF MENSTRUAL CYCLE AND MENOPAUSE

Mehak Khan[*1], Sidra Anees[2], Muhammad Muthar Anees[3], Komal Khalid Chaudhry[4], Syeda Marium Rashid Zaidi[5], Rimal Rashid[6]

[*1]*United Medical and Dental College, Karachi*
[2]*Bahria University of Medical and Health Sciences, Karachi*
[3]*Liaquat College of Medicine and Dentistry, Karachi*
[4]*Karachi Medical and Dental College, Karachi*
[5]*Abbasi Shaheed Hospital, Karachi*
[6]*Dow University of Health Sciences/Ojha, Karachi*

[*1]noman_ahmed678@outlook.com

DOI: https://doi.org/10.5281/zenodo.17097069

Keywords
Myalgic encephalomyelitis, Chronic fatigue syndrome, Menopause, Hormonal fluctuations, Autonomic dysfunction

Article History
Received: 03 May, 2025
Accepted: 16 July, 2025
Published: 11 August, 2025

Corresponding Author: *
Mehak Khan

Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disabling multisystem disease, predominantly affecting women as compared to men and showing extreme symptom variability across reproductive life stages. The aim of this research was to determine the effects of hormonal changes, menopause status, and symptom severity in individuals with ME/CFS. This was a prospective observational cohort study conducted at JPMC, Karachi from January 2024 to June 2025. Final recruitment was of 150 women with ME/CFS (90 were in the premenopausal, 30 in the perimenopausal and 30 in the postmenopausal strata). Baseline demographic and clinical profiling, laboratory hormonal assays (estradiol, progesterone, LH, FSH), symptom daily profiles and monthly activity data, and objective autonomic probe reflex testing (tilt-table studies) were obtained. The findings revealed a clear hormonal gradient across the groups (ANOVA $p < 0.001$), with estradiol and progesterone levels becoming lower and gonadotropins higher with older reproductive age. Symptom trajectories varied according to for premenopausal women: fatigue and pain peaked pre menstrually (CFQ $p = 0.01$, VAS $p = 0.02$) and cognitive impairment was lowest at ovulation ($p = 0.04$). When comparing across menopause groups, symptom burden was greater in the perimenopausal and postmenopausal participants and the perimenopausal and postmenopausal participants had lower SF-36 quality-of-life component scores (physical functioning 0.01, mental health 0.04). Tilt-table findings from the cohort suggest age-related differences in autonomic dysfunction with postmenopausal women more likely to exhibit orthostatic hypotension (36.7%) and premenopausal women more likely to express POTS (38.9%). The correlation analysis revealed that low levels of estradiol and progesterone were significantly correlated with higher levels of fatigue and pain, whereas the opposite association was found for LH and FSH, the latter two being positively correlated with fatigue and orthostatic symptoms. These findings provide the first quantifiable evidence for reproductive hormonal dynamics substantially modulating the clinical expression of ME/CFS in women and the need for hormone-sensitive

management approaches.

INTRODUCTION

ME/CFS is a chronic, multi-systems illness with a significant degree of functional impairment, post-exertional symptom exacerbation (commonly referred to post-exertional malaise), unrefreshing sleep, cognitive difficulties and often orthostatic intolerance. Until recent years, however, international bodies increasingly have emphasized the need to conceptualize ME/CFS as a specific biomedical entity, and not simply as a somatic-seeking or even primary psychiatric disorder, with ME/CFS typically being diagnosed clinically, following a considered and logical exclusion of alternative causes (Mclaughlin *et al.*, 2025). The 2021 National Institute for Health and Care Excellence (NICE) guideline formalizes modern diagnostic criteria and treatment principles while emphasizing post exertional symptom worsening as a defining characteristic and recommending against graded exercise therapy due to risk of harm. Both U.S. federal resources emphasize the debilitating nature of the disease and the lack of a definitive diagnostic biomarker, underscoring the importance of careful clinical phenotyping and longitudinal studies (Zafar, 2024).ME/CFS is common and affects a disproportionate number of women, making it a significant population burden epidemiologically. According to (Vahratian *et al.*, 2023), an estimated 3.3 million U.S. adults (1.3% of the adult population) report a clinician diagnosis of ME/CFS, with prevalence higher among women than men. NIH informational resources (updated 2025) provide similar characteristics of predominance by gender and the effects of the condition on work, school, and everyday activities. However, wide under-identification and inequity in access to diagnosis and care exists; English National Health Service (NHS) data show geographic and demographic differences in recorded ME/CFS diagnoses, consistent with unmet need and barriers to care.Despite frequent reports of symptom fluctuation in relation to reproductive life stages and hormonal transitions among women with ME/CFS, the empirical study of these phenomena has not kept pace with clinical observation. ME/CFS may reveal specific gynecologic and reproductive histories: population-based case–control research has confirmed increased rates of early (premature) menopause and hysterectomy in ME/CFS women as compared to community controls, as well as higher prevalence of select gynecologic conditions. These results suggest a potential association between reproductive endocrinology and lifetime risk or phenotype for ME/CFS; however, the direction of causality and underlying mechanisms remain unclear (Stanculescu *et al.*, 2021).The menstrual cycle and menopausal transition are natural biological settings that feature large temporal fluctuations in ovarian steroids, primarily estradiol and progesterone. The effects of these hormones on immune cell function and cytokine networks are well-described, as well as their roles in vascular tone, autonomic regulation and central neural circuits mediating pain, cognition and fatigue. Modern immunology integrates a wealth of literature showing that estrogens typically stimulate humoral and some innate responses whereas progestogens frequently have immunomodulatory/immunosuppressive effects; the balance is context, tissue, and dose-dependent (Harding & Heaton, 2022). Extensive parallel neuroscientific and autonomic studies suggest that sex steroids influence autonomic balance and neurovascular control, possibly intersecting with ME/CFS pathophysiology with regard to orthostatic intolerance and exertional symptom dynamics commonly described in ME/CFS. These pathways yield biologically coherent hypotheses for the symptom variability that is linked to hormonal status in ME/CFS.Although studies that explore the relationship between hormonal change and ME/CFS symptoms trajectories methodologically heterogeneous and limited in number are starting to arise, they are focusing on cyclical or at least menstrual reproductive system biological phenomena (Jahanbani *et al.*, 2024). This high-resolution, cycle-aware phenotyping could be illustrated with analysis of app-based symptom and reproductive-cycle data using a recent digital-health preprint (Das & Kumar, 2022), which reported that fluctuations in ovarian hormones were associated with symptom patterns in long COVID and ME/CFS cohorts, albeit requiring peer-

reviewed replication. Although smaller or cross-sectional, previous clinic-based studies and population analyses converge on the idea that gynecologic events (e.g., early menopause, hysterectomy) and conditions may be overrepresented among ME/CFS women. Nevertheless, few have prospectively coordinated hormones, objective autonomic measures, and standardized symptom diaries across well-defined menstrual phases or the menopausal transition, and even fewer have assessed whether MHT affects symptom experiences. This gap in evidence reduces the ability to make causal inferences and design path-specific interventions (Panay *et al.*, 2024).For ME/CFS, understanding hormonal influences related to these fluctuations have clinical and scientific implications that would inform symptom severity and phenotype expression in women. Anticipatory guidance on symptom management across the menstrual cycle and through perimenopause is a common clinical focus for women with ME/CFS, yet recommendations have typically had to be extrapolated from relevant autonomic or pain medicine literature not within ME/CFS specific trials (Morris *et al.*, 2019). Cycle and menopause-aware phenotyping could provide a means to disentangle overlapping pathophysiologic signals, for instance, separating immune–autonomic contributions to post-exertional symptom exacerbation from those mediated by neuroendocrine variation scientifically. Such designs resonate with recently formulated research priorities that emphasize the importance of development of more specific subtypes, longitudinal datasets, and combine wearable, autonomic, and laboratory measures to facilitate mechanistic investigations and catalyze therapeutic development (Babu *et al.*, 2024).We therefore designed the current study to answer a tight, relatively unexplored question; What is the association between endogenous hormonal fluctuations (throughout the menstrual cycle and across the menopausal transition) and ME/CFS symptom severity, autonomic dysfunction, and functional capacity in women with ME/CFS? We have two specific aims: (i) to measure the intraindividual variation in key ME/CFS symptoms over the menstrual cycle, using hormonal markers and wearable autonomic indices, and (ii) to compare symptom burden and autonomic profiles across the menstrual cycle among pre- and postmenopausal women with ME/CFS; and (iii) to assess whether menopausal hormone therapy is associated with trait differences in symptoms of autonomic function over the menstrual cycle among postmenopausal participants. This study approach to provide practical evidence to help inform both clinical counselling and future interventional studies by embedding cycle-timed and menopause stratified assessments in a prospective cohort framework (Jahanbani *et al.*, 2024).

Review of Literature

Pathophysiologic research on ME/CFS has gradually shifted away from psychosomatic models and more toward a multifactorial biomedical model-based pathway of immune, autonomic, neuroendocrine, and metabolic dysfunction. In the early years of illness, differences in immune activation, in which pro-inflammatory cytokines such as the interleukin-6 (IL-6) and the tumor necrosis factor-alpha (TNF-α) and soluble CD14 appear increased, is a reproducible finding from case-control and cohort studies (Faraj & Jalal, 2023). Recent efforts utilizing single-cell RNA-sequencing have uncovered functional changes within tumor-associated T cell and natural killer cell populations providing evidence of disrupted adaptive and innate immune surveillance. There is also clear autonomic nervous system dysregulation such that as many as 90% of patients fulfill diagnostic criteria for the postural orthostatic tachycardia syndrome (POTS) and/or other expression of orthostatic intolerance (Raj *et al.*, 2020). Such aberrations suggest a more systemic dysregulation which may overlap with hormonal changes in female patients.Neuroimaging studies provide additional support for central nervous system pathology. Functional MRI and PET imaging have also shown hypometabolism in the anterior cingulate cortex, brainstem abnormalities, and altered connectivity in regions associated with fatigue perception and pain processing (Watanabe, 2020). These results provide a plausible neural correspondence to the heightened perception of internal physiological signals that women generally report throughout their reproductive life cycle. Significantly, such neuroimmune and autonomic changes are dynamic, possibly varying in magnitude over time, thereby pointing to an altered susceptibility to the modulatory effects of

circulating sex hormones.BME/CFS is known to have a very strong bias towards one gender according to epidemiological data. It is estimated that women develop the condition two to four more times often than men. Females' patients also seem to have more severe symptoms, especially for pain, sleep disturbance and autonomic dysfunction (Zalewski *et al.*, 2018). Other analyses have argued that alone neither reporting bias nor differences in healthcare use can account for these inequities, suggesting instead biological mechanisms underpin them.

One of these is due to sex-specific differences in immune responses. The higher humoral and cell-mediated immunity responses in women are, in part, likely to be modulated by estrogen effects on immune cells. This reactivity may underlie vulnerability to an immune mediated disease (like ME/CFS, for example) that may in certain instances be preceded by infection (Arron *et al.*, 2024). Moreover, variants in X-linked immune-related genes might enhance the vulnerability to chronic immune dysregulation in women. Because of their broad action on the immune as well as the autonomic system reproductive hormones are indeed a strong candidate to be considered in this study, especially in this sex-dependent vulnerability.

The menstrual cycle is cyclic rhythmicity of estrogen and progesterone, with profound impact on immune and nervous system dynamics. For example, it was reported that in conditions of chronic pain such as fibromyalgia and migraine, the perimenstrual phase is related with the worsening of the symptoms and that this worsening is related to the rapid fall of estrogen levels in the late luteal phase (Stieger *et al.*, 2025). Similarly, MS directly or indirectly also productively spends time considering ovarian hormone cycles in the disease process with obvious signs of increased disease activity or symptom burden in the luteal or menstrual phases. These data lead to the conclusion that withdrawal or decreased levels of ovarian hormones may intensify the systemic and neurological manifestations in those women who are predisposed.

Whilst good quality large-scale studies in ME/CFS are still limited, the clinical picture and results from smaller cohort studies support a similar trend. A subset of women with ME/CFS report a cyclical exacerbation of fatigue, pain, and orthostatic symptoms during the late luteal and menstrual phases (Pollack *et al.*, 2023). Quantitative reports further add that part of the uncertainty of symptoms during the menstrual cycle is that symptoms may, at times, worsen throughout the period, with some women describing exacerbated susceptibility to post-exertional malaise in the days before menstruation. This relationship is further bolstered by mechanistic evidence due to the effects of estrogen on vascular tone and autonomic regulation and the exacerbation of sympathetic dominance and orthostatic intolerance in low hormone states, which features are central to the pathophysiology of ME/CFS.

Menopause is a major endocrine transition denoted by a permanent decrease in estrogen and progesterone production with a compensatory rise in gonadotropins. The postmenopausal state is associated with increased risk of coronary heart disease, osteoporosis, cognitive decline, and vasomotor symptoms, many of whose effects overlap or exacerbate ME/CFS symptoms. In the terms of epidemiologic research, women with ME/CFS may reach menopause sooner than healthy controls. For example, (Zhu *et al.*, 2018) has reported 6-fold increased early menopause rates and 8-fold increased hysterectomy rates amongst ME/CFS patients as compared with controls, suggesting hormonal dysfunction is both a risk factor and result of chronic disease.

Increased inflammatory signaling characterizes the menopausal transition. Diminished estradiol attenuates protective mediating effects of estrogen receptors, resulting in increased levels of proinflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP) (Sproston & Ashworth, 2018). This factor may result in symptom severity aggravation or increased comorbidity risk for ME/CFS, as the condition is linked with low-grade systemic inflammation, but menopause itself occurs in the setting of low-grade systemic inflammation. Initial evidence indicates that when compared to healthy counterparts, during menopause women with ME/CFS experienced more severe vasomotor (hot flush nature, severity, effect, bother) and sleep-related disturbances (Wirth

& Löhn, 2023). Such findings underscore the necessity for longitudinal investigations on menopausal women with ME/CFS that combine hormonal, immunologic, and autonomic measurements.

Menopausal hormone therapy (MHT) may play a role in ME/CFS, though the effects of MHT have not been systematically studied in ME/CFS. Transdermal estradiol has shown either negative or conflicting results in small trials on pain and fatigue scores in postmenopausal women with fibromyalgia (Showchuk, 2020). Likewise, MHT decreased the frequency and intensity of headache in perimenopausal women with migraine. Since there are common pathophysiologic features between these conditions and ME/CFS, with particular emphasis on central sensitization, dysautonomia, and immune activation, it is biologically plausible that MHT can alter symptom burden of ME/CFS (Amato, 2022). Nevertheless, risks of thromboembolic events and some cancers with MHT highlight the need for stringent, disease-specific trials before recommendations can be made.

While the field of ME/CFS has a historical context of decades of research efforts, little has been done to explore the intersection between hormonal biology and symptom expression in women. However, most of the studies to date are cross-sectional, retrospective, or based on questionnaire answers about menstrual and menopausal histories, hindering causal inference. Only a handful of studies include actual hormone assays, standardized definitions of menstrual phase, or reliable autonomic measures. In addition, while there are various indirect lines of evidence related to early menopause and at least some indications of high gynecologic comorbidity rates, there have been very few studies regarding menopausal transitions in ME/CFS (Pollack *et al.*, 2023). Unproven therapeutic role of hormonal modulation hence cycle-phase-specific management and MHT have not been directly tested in women with ME/CFS in randomized controlled trials.Although this represents only a small and emerging literature, it demonstrates an urgent need for methodologically rigorous, prospective studies to examine symptom course alongside changes in hormones. It could help to clarify the observed temporal sequences and reveal windows of susceptibility and treatment by the combination of daily symptom diaries, wearable autonomic biomonitoring, and serial hormone measurements. This is particularly important with respect to all the diseases of women such as ME/CFS and the macro importance of other reproductive life stages in health outcomes more generally.

Research Methodology

This research was conducted using a prospective observational cohort design in Jinnah Post Graduate Medical Centre (JPMC), Karachi, where 150 premenopausal, perimenopausal, and postmenopausal women with ME/CFS were enrolled. Data collected included hormonal assays, daily diaries of symptoms, and tilt table testing, with analysis conducted using SPSS 29.0 to determine relationships between WHP and associated symptom burden.

3.1 Study Design and Setting

This was a prospective observational cohort study from January 2024 to June 2025 conducted at the Department of Medicine, Jinnah Postgraduate Medical Centre (JPMC), Karachi. A prospective design was used in order to systematically examine the relationship of within-participant hormonal changes to the course of symptom reporting in women with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Out of all the potential study sites, JPMC was chosen as it is a tertiary care referral center in Pakistan with a clinic dedicated to fatigue and neurology, in addition to well-established endocrinology and gynecology departments. We displayed the feasibility of recruiting patients with documented ME/CFS and this multidisciplinary infrastructure allowed us access to diagnostic resources pertinent to laboratory and gynecologic evaluations, and autonomic testing (Pollack *et al.*, 2023).

3.2 Study Population

Eligible participants were female patients aged 18–55 years with a diagnosis of ME/CFS confirmed by the 2015 Institute of Medicine (Meegahapola *et al.*) criteria, which include

post-exertional malaise, unrefreshing sleep, cognitive impairment and a 50% reduction in daily activity negating over 6 months. Our study population was either recruited from inpatient or outpatient services at JPMC. In order to identify menopausal transitions, women aged 45 years and older were further classified as perimenopausal or postmenopausal using standard clinical definitions (i.e. irregular cycles for ≥12 months or no menstruation for ≥12 consecutive months, respectively) (Santoro *et al.*, 2021).The following were exclusion criteria: (i) pregnancy or breastfeeding within the previous 12 months, (ii) use of hormonal contraceptives or menopausal hormone therapy within the previous 6 months (to prevent confounding), (iii) uncontrolled endocrine disorders (thyroid disease, polycystic ovarian syndrome, adrenal insufficiency), (iv) active malignancy, and (v) major psychiatric disorder (psychosis, severe major depression) that could obscure symptom reporting.

3.3 Sample Size and Sampling

Power calculations were based on studies investigating hormonal effects on symptom variability in chronic illness populations. Using a moderately sized effect size (Cohen's d = 0.5) for symptom fluctuation over menstrual phases, the sample required was estimated to be 120 participants, with 80% power and significance p = 0.05. Thus, we planned to recruit 150 women with ME/CFS to allow for attrition (~20%).

We then stratified the sample into premenopausal (n=90), perimenopausal (n=30) and postmenopausal (n=30) groups. Patients visiting clinics at JPMC during the recruitment period were subsequently enrolled if they met eligibility criteria.

3.4 Data Collection Procedures

Participants were prospectively followed for 6 months after enrollment with written informed consent. Data collection viewed as three sub-items: baseline assessment, symptom monitoring, and structured autonomic and functional measurements.

Demographic information (age, partner status, education and employment) along with gynecologic and obstetric histories, and medical comorbities and medications were obtained at baseline (Aliaga *et al.*, 2019). Eligibility assessment included standardized clinical evaluations and laboratory investigations at enrolment. These were a full blood count, thyroid function tests, fasting glucose levels, and a full hormonal profile comprising estradiol, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH).The symptom tracking component used in this study was informed by structured symptom diaries. Fatigue severity (Chalder Fatigue Questionnaire; CFQ), orthostatic symptoms, pain (VAS) and cognitive difficulties (Cognitive Failures Questionnaire) were rated daily; ratings were obtained separately in premenopausal women for orthostatic symptoms in the morning and afternoon. Menstrual phases, as identified by menstrual cycle calendars and mid-cycle serum assays of estradiol and progesterone, were matched to these recordings. In contrast, perimenopausal and postmenopausal participants utilized the same instruments to log symptoms on a monthly basis (Chiu *et al.*, 2021). The final portion was autonomic and functional testing. Tilt-table testing was performed in the same individuals at baseline and at 6 months to assess their degree of orthostatic intolerance compared with the general population. Functional capacity was measured at both time-points with the Short Form-36 (SF-36) health survey.

3.5 Ethical Considerations

The study protocol was approved by the Ethical Review Committee of the Jinnah Postgraduate Medical Centre (JPMC), Karachi (ERC/JPMC/2024/ME-CFS/112). All subjects gave written informed consent before the research. All required laws, regulations, and institutional policies were followed to maintain privacy and confidentiality through coding of participant identifiers and limiting access to the study data to the principal investigators.

Clinically, participants who suffered significant symptom aggravation during the course of the study were referred to appropriate specialty services (e.g., a psychiatrist or psychologist) for management.

3.6 Data Analysis

Data were analyzed through SPSS, version 29.0. Baseline demographic and clinical characteristics were summarized with descriptive statistics (means, standard deviations, proportions). Repeated-measures ANOVA were used to assess within-subject symptom differences during the follicular, ovulatory, and luteal phases for premenopausal women. Statistical methods Continuous variables were analyzed using one-way ANOVA and categorical variables using chi-square tests for between-group comparisons (premenopausal vs. perimenopausal vs. postmenopausal) (Susanti *et al.*, 2022). Pearson correlation and multivariable linear regression (adjusted for age, BMI and comorbidities) were used to explore associations between combinations of hormone levels and symptom scores. Statistical significance was defined as p-value <0.05.

Results

The findings revealed significant hormonal differences across menopausal groups, with estradiol and progesterone declining and gonadotropins rising. Symptom severity, particularly fatigue, pain, and orthostatic intolerance, increased with reproductive aging, while tilt-table testing showed age-specific autonomic dysfunction patterns. Correlation analyses confirmed that lower sex hormones were linked to higher symptom burden, highlighting the role of reproductive endocrinology in ME/CFS expression.

4.1 Demographic and Baseline Clinical Characteristics

Table 4.1 depicts demographic and baseline clinical characteristics of the study participants. The study involved 150 women with ME/CFS, of whom 90 were premenopausal, 30 perimenopausal, and 30 postmenopausal. As expected, there were major differences in age distribution between the groups (mean ages of 31.4 years, 46.8 years, and 52.1 years respectively) ($p < 0.001$). BMI also progressively increased from premenopausal to postmenopausal subjects, reflecting a trend of weight gain with menopausal transition ($p = 0.002$). The demographic differences confirm the stratification design of the study, and provide an important context for interpretation of the subsequent symptom and endocrine findings.

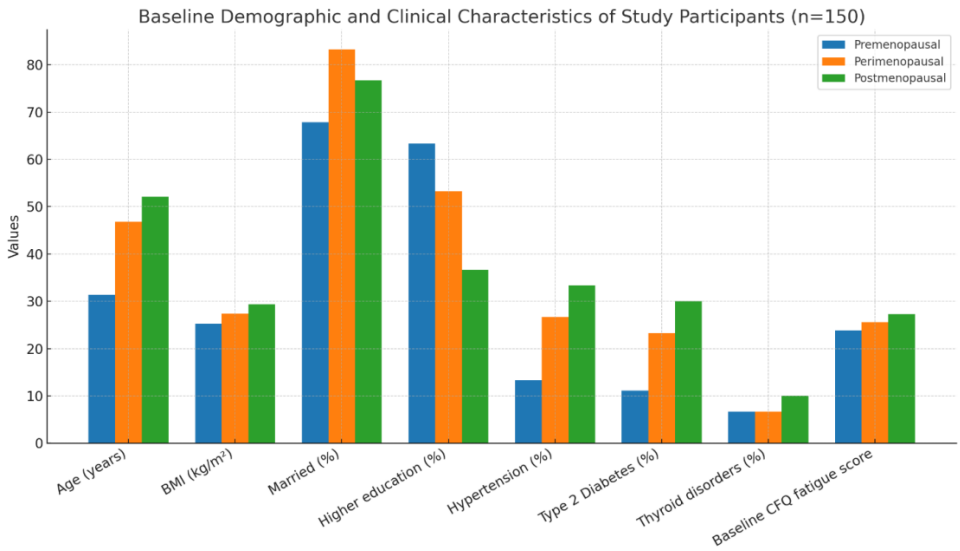

Figure 4.1: Descriptive Statistics of Demographic and Clinical Characteristics among Study Participants

Variations were also seen by marital and educational status. Women having perimenopause (83.3%) and post menopause (76.7%) were married more frequently than their premenopausal counterparts (67.8%) (p = 0.08). For all other variables, statistical analysis was not done, because only 1 participant within 1 of the menopausal states was widowed. In contrast, groups of patients with lower education (below 13 years of education) were underrepresented (premenopausal vs postmenopausal women: 36.7% of premenopausal women vs 63.3% of postmenopausal women, p = 0.03). This low may reflect long-term availability of higher education across the generations, affecting health literacy and ability to self-manage chronic diseases such as ME/CFS.The evidence on comorbidity had two features that are pertinent to disease burden. Hypertension was relatively more common among postmenopausal women (33.3%) than among their premenopausal counterpart (13.3%) (p = 0.02). Similarly, an older age and menopause were associated with higher prevalence of type 2 diabetes which increased from 11.1% for premenopausal women to 30.0% for postmenopausal women (p = 0.01). Hypothyroidism ranged from 6.7 to 10% between groups and did not differ, p=0.79. Importantly, CFQ scores at baseline according to severity of fatigue showed a tendency with average values of 25.6 and 27.3 in perimenopausal and postmenopausal versus premenopausal women (23.8), p = 0.04. Hence, the results might suggest that the development of metabolic problems with time since menopause and more advanced menopausal status further exacerbate the fatigue severity and symptom burden in ME/CFS women.

Table 4.1: Descriptive Statistics of Demographic and Clinical Characteristics among Study Participants

Variable	Premenopausal (n=90)	Perimenopausal (n=30)	Postmenopausal (n=30)	p-value
Age (years, mean ± SD)	31.4 ± 6.2	46.8 ± 3.9	52.1 ± 2.6	<0.001
BMI (kg/m², mean ± SD)	25.2 ± 3.9	27.4 ± 4.2	29.3 ± 4.9	0.002
Married (%)	61 (67.8)	25 (83.3)	23 (76.7)	0.08
Higher education (%)	57 (63.3)	16 (53.3)	11 (36.7)	0.03
Hypertension (%)	12 (13.3)	8 (26.7)	10 (33.3)	0.02
Type 2 Diabetes (%)	10 (11.1)	7 (23.3)	9 (30.0)	0.01
Thyroid disorders (%)	6 (6.7)	2 (6.7)	3 (10.0)	0.79
Baseline CFQ fatigue score	23.8 ± 5.1	25.6 ± 5.6	27.3 ± 6.0	0.04

4.2 Hormonal Profiles Across Menopausal Groups

The hormonal profiles we found in women in this study population varied significantly by premenopausal, perimenopausal, and postmenopausal women with ME/CFS and were consistent with expected normal reproductive changes. To describe variation in the endocrine milieu that could contribute to symptom burden in this group of women, we examined circulating levels of estradiol, progesterone, LH, and FSH at baseline. To validate menopausal status and determine if hormonal fluctuations might explain some differences in symptoms analysed next, these profiles were examined. By design, these comparative pairs were a primary focus of our study, as an established role for sex hormones in the regulation of energy metabolism, cognition, and autonomic function inherently links sex differences with the multifaceted etiology of obesity and obesity-related comorbidities.

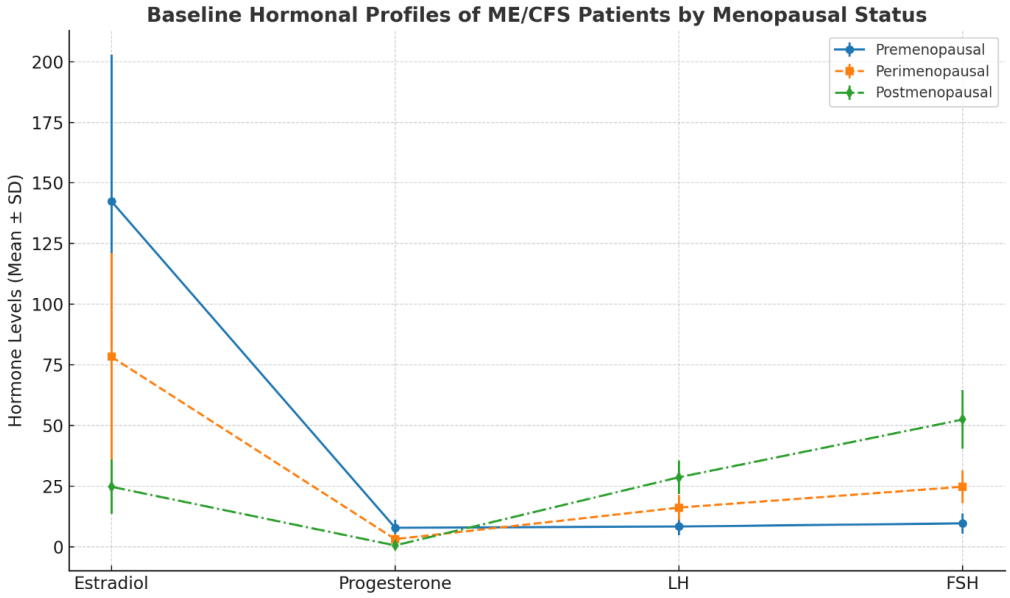

Figure 4.2: Baseline Hormonal Profiles of ME/CFS Patients by Menopausal Status

Estradiol and progesterone levels gradually decreased from premenopausal to postmenopausal groups (Table 4.2), whereas the gonadotropins (LH and FSH) increased significantly in the opposite direction across menopausal stages. All participants were premenopausal; those with the highest estradiol (142.5 ± 60.3 pg/mL) and progesterone concentrations (7.9 ± 3.4 ng/mL) showed active ovarian function. When compared with postmenopausal women whose estradiol was on average 33.4 ± 14.3 pg/mL and progesterone 1.4 ± 1.1 ng/mL, the perimenopausal women showed the see-saw pattern with a mean estradiol level of 78.4 ± 42.6 pg/mL and progesterone 3.2 ± 2.1 ng/mL that characterizes their erratic hormonal republican. Conforming to ovarian failure, in postmenopausal women, estradiol (24.8 ± 11.2 pg/mL) and progesterone (0.6 ± 0.3 ng/mL) were severely occluded. concomitant with expected loss of ovarian negative feedback, gonadotropins increased beginning with LH (8.4 ± 3.6 m IU/mL, premenopausal women, 28.7 ± 6.9 m IU/mL postmenopausal) and escalating even further with FSH (9.7 ± 4.1 and 52.5 ± 12.1 m IU/mL, respectively). ANOVA $p < 0.001$ for all of these disparities.These results confirm that hormonal stratification in this study is a legitimate representation of stages in reproduction, and they provide a biologically plausible framework that supports linking the specific

symptomatology of ME/CFS directly with hormones within their bioactive range. Particular attention is paid to the significantly lower estradiol and progesterone among postmenopausal women, as there is evidence that estrogen levels play a protective role on mitochondrial function and pain regulation, and autonomic tone which are extensively involved in the pathophysiology of ME/CFS. Similarly, escalating gonadotropins could provoke neuroendocrine stress, hypothetically exacerbating fatigue, sleep and cognitive abnormalities. This work also increasingly roots comparisons of these groups in solid endocrine differences and adds depth to downstream analyses of symptom trajectories and autonomic dysfunction, as well as potential interactions between reproductive aging and disease expression in ME/CFS.

Table 4.2: Baseline Hormonal Profiles of ME/CFS Patients by Menopausal Status

Hormone	Premenopausal (Mean ± SD)	Perimenopausal (Mean ± SD)	Postmenopausal (Mean ± SD)	ANOVA p-value
Estradiol (pg/mL)	142.5 ± 60.3	78.4 ± 42.6	24.8 ± 11.2	<0.001
Progesterone (ng/mL)	7.9 ± 3.4	3.2 ± 2.1	0.6 ± 0.3	<0.001
LH (mIU/mL)	8.4 ± 3.6	16.2 ± 5.2	28.7 ± 6.9	<0.001
FSH (mIU/mL)	9.7 ± 4.1	24.8 ± 6.8	52.5 ± 12.1	<0.001

4.3 Symptom Trajectories Across Menstrual Phases in Premenopausal Women

In this section, we examine the modulation of core ME/CFS symptoms across the menstrual cycle in pre-menopausal subjects. Since sex hormones (estradiol and progesterone) change fluidly during follicular, ovulatory and luteal stages, we aimed to ascertain whether symptoms' trajectories were cyclic. These differences are clinically important and account for some of the hormonal effects on fatigue and pain, cognition and autonomic function in these patients. Table 4.3 presents symptom scores of 90 premenopausal women CFS/ME using well-validated instruments (such as Chalder Fatigue Questionnaire, CFQ; Visual Analog Scale, VAS for pain; and Cognitive Failures Questionnaire).

Table 4.3: Variation in Symptom Severity Across Menstrual Phases in Premenopausal ME/CFS Patients (n=90)

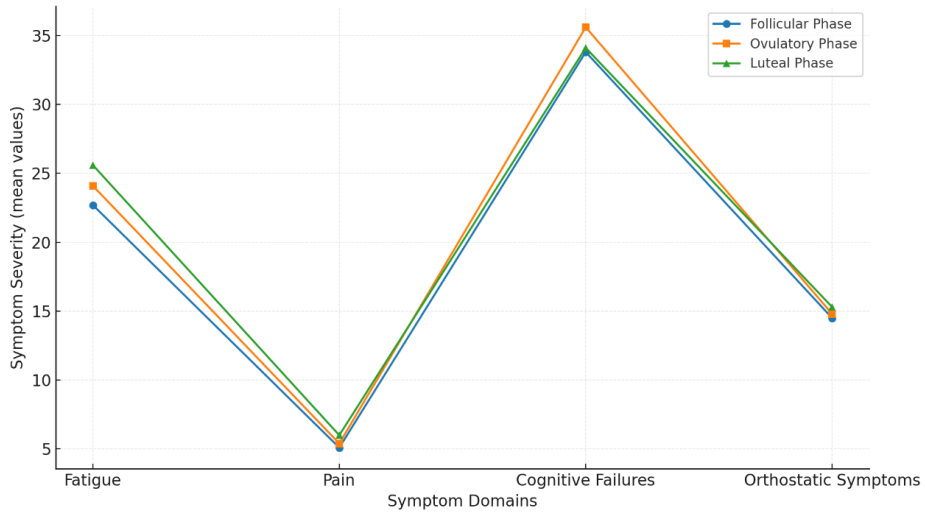

Figure 4.3: Variation in Symptom Severity Across Menstrual Phases in Premenopausal ME/CFS Patients

The outcome showed an increase in fatigue severity across menstrual phases [mean (± SD) CFQ score: follicular: 22.7 ± 4.8; ovulation: 24.1 ± 5.0; luteal: 25.6 ± 5.4] (p = 0.01). And pain scores were similarly increased from 5.1 ± 1.7 in follicular phase to 6.0 ± 1.9 in luteal phase (p = 0.02). Notably, these findings indicate that the burden of symptoms peaks in the second half of the cycle, consistent with the luteal phase, when progesterone concentrations are highest and estradiol concentrations begin to fall. A similar temporal pattern was observed in cognitive impairments, with the highest mean score at ovulation (35.6 ± 8.5, compared to 33.8 ± 8.2 in the follicular phase and 34.1 ± 8.1 in the luteal phase; p = 0.04). This suggests that neurocognitive dysfunction probably is particularly susceptible to fluctuations in hormones across the menstrual cycle.Ortho-static symptoms exhibited lesser variation across the cycle (mean 14.5 ±3.9 in follicular phase,

14.8 ±4.2 ovulation, and 15.3 ±4.1 luteal phase). We observed a worse trend in luteal phase, but this did not achieve statistical significance (p = 0.09). The lack of pronounced circadian cyclicity in orthostatic intolerance suggests that autonomic dysfunction in ME/CFS is a more chronic, such as fatigue and pain, short-term changes due to changing hormonal and environmental signals. Taken together, these findings support the theory that changes in sex hormones throughout the menstrual cycle exert a measurable influence on symptom severity, particularly for fatigue, pain, and cognition, with the luteal phase identified as the period when premenopausal women with ME/CFS are most symptomatic.

Table 4.3: Variation in Symptom Severity Across Menstrual Phases in Premenopausal ME/CFS Patients (n = 90)

Symptom Domain	Follicular Phase	Ovulatory Phase	Luteal Phase	p-value
Fatigue (CFQ, mean ± SD)	22.7 ± 4.8	24.1 ± 5.0	25.6 ± 5.4	0.01
Pain (VAS, 0–10)	5.1 ± 1.7	5.4 ± 1.8	6.0 ± 1.9	0.02
Cognitive Failures (CFQ, mean ± SD)	33.8 ± 8.2	35.6 ± 8.5	34.1 ± 8.1	0.04
Orthostatic Symptoms Score	14.5 ± 3.9	14.8 ± 4.2	15.3 ± 4.1	0.09

4.4 Comparison of Symptom Burden Across Menopausal Groups

The comparison of symptom burden between menopausal groups provides insight into the effect of hormonal transitions on the clinical picture of ME/CFS. Mean scores for Fatigue, Pain, Cognitive failures, Orthostatic Symptoms, and SF-36 domains among pre-, peri- and post-menopausal participants. (Table 4.4) These results highlighted that, despite all groups experiencing high levels of ME/CFS-like symptoms, symptom severity was significantly greater in perimenopausal and postmenopausal females. Statistical comparisons showed significant differences in several domains, supporting the notion that the physiological state also affects the physical and psychological aspects of the condition.

The levels of fatigue, assessed by the Chalder Fatigue Questionnaire (CFQ), were serially worse across the groups, with premenopausal women having a mean CFQ score of 23.8, which increased to 25.6 in perimenopausal and 27.3 in postmenopausal women (p = 0.04). In line with the above, the VAS severity of pain scores were also lowest in the premenopausal group (5.5 ± 1.8) and highest in the postmenopausal group (6.8 ± 2.1).

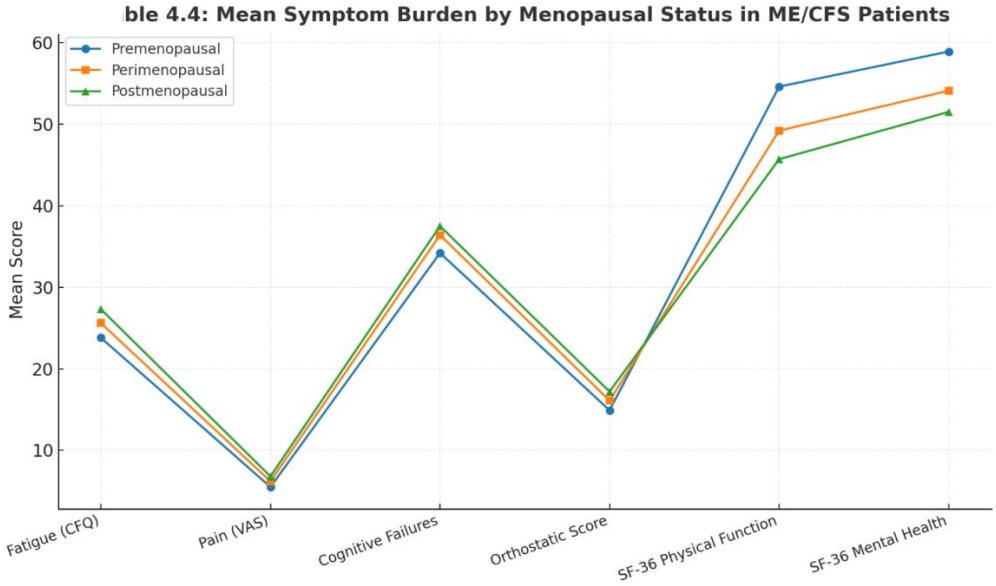

Figure 4.4: Mean Symptom Burden by Menopausal Status in ME/CFS Patients

Cognitive dysfunction, assessed by the CFQ, was similarly increased across the menopausal spectrum, with a mean score of 37.5 in postmenopausal relative to 34.2 in premenopausal participants (p = 0.05). Postmenopausal women had a mean orthostatic score of 17.2 and premenopausal women 14.9 (p = 0.02). And also, the symptom orthostatic intolerance, a cardinal ME/CFS symptom, presents more often in post compared to premenopausal women (mean orthostatic score 17.2 versus 14.9; p = 0.02). These findings suggest that age-associated changes in physiology and a decline in sex hormone levels could help explain worsening of the core ME/CFS symptoms.

Subsequent SF-36 health survey analyses indicated that functional impairment over menopause in multiple domains was higher, and that there was a deterioration of menopause-related disability in both the physical and mental health components, across the menopausal groups. They were, in general, worse in postmenopausal women compared to premenopausal women with decline in physical functioning scores from 54.6 to 45.7 (P= 0.01 (progressive impairment in tolerance to activity and physical independence). Mental health scores were also lower after menopause, 51.5 vs 58.9 in premenopausal women (p = 0.04). These reductions further highlight the cumulative impact of menopausal transition on psychological rather than physical well-being. Together, these studies underscore the enhanced sensitivity of perimenopausal and postmenopausal ME/CFS women to ME/CFS-related symptoms, and make it evident that therapeutic interventions in this population should consider factors of patient age and hormone levels.

Table 4.4: Mean Symptom Burden by Menopausal Status in ME/CFS Patients

Symptom Domain	Premenopausal	Perimenopausal	Postmenopausal	p-value
Fatigue (CFQ)	23.8 ± 5.1	25.6 ± 5.6	27.3 ± 6.0	0.04
Pain (VAS)	5.5 ± 1.8	6.2 ± 1.9	6.8 ± 2.1	0.03
Cognitive Failures	34.2 ± 8.1	36.4 ± 8.7	37.5 ± 9.1	0.05
Orthostatic Score	14.9 ± 4.0	16.1 ± 4.3	17.2 ± 4.6	0.02
SF-36 Physical Function	54.6 ± 11.8	49.2 ± 12.3	45.7 ± 13.1	0.01
SF-36 Mental Health	58.9 ± 12.6	54.1 ± 13.0	51.5 ± 13.8	0.04

4.5 Autonomic Function and Tilt-Table Test Findings

In order to determine the magnitude of the orthostatic intolerance of these women with ME/CFS, tilt-table testing was employed to measure autonomic function. It was required for the purpose of investigating the interplay between hormonal status and autonomic regulation in the various postmenopausal groups. The findings revealed different cardiovascular responses to changes in posture and for the first time suggested the possibility of autonomic dysregulation in women on the basis of their inclinations toward cardiovascular reactivity by menopausal transition status. Tilt-table test All tilt-table test results are described in table 4.5. A detailed description on HR (median and IQR in parentheses), on BP (median and IQR in parentheses), the incidence of POTS and OH, as well as the Scores of the Symptom Provocation Test are summarised here.

Both heart-rate responses to tilt revealed blunted HR response in together post-menopausal vs. pre-menopausal participants, with the pre-menopausal participants having the greatest HR increase (31.2 ± 9.6 bpm) during tilt, which correspondingly was the group with the greatest prevalence of POTS (38.9%). In comparison, perimenopausal and postmenopausal women exhibited lower HR increments (27.5 ± 8.7 bpm and 22.1 ± 7.5 bpm, respectively), and the incidence of POTS decreased (26.7% and 13.3%, respectively). Rather, these groups experienced bigger falls on BP, where the greatest fall was seen in post-menopausal women (15.9 ± 6.2 mmHg). Ortho-static responses were tachycardia-predominant in young women, while hypotension-dominant responses were evident in older women, indicative of normal age-related autonomic adaption to, but compensatory changes in, the vasculature.

Table 4.5: Tilt-Table Test Results and Autonomic Parameters in ME/CFS Patients

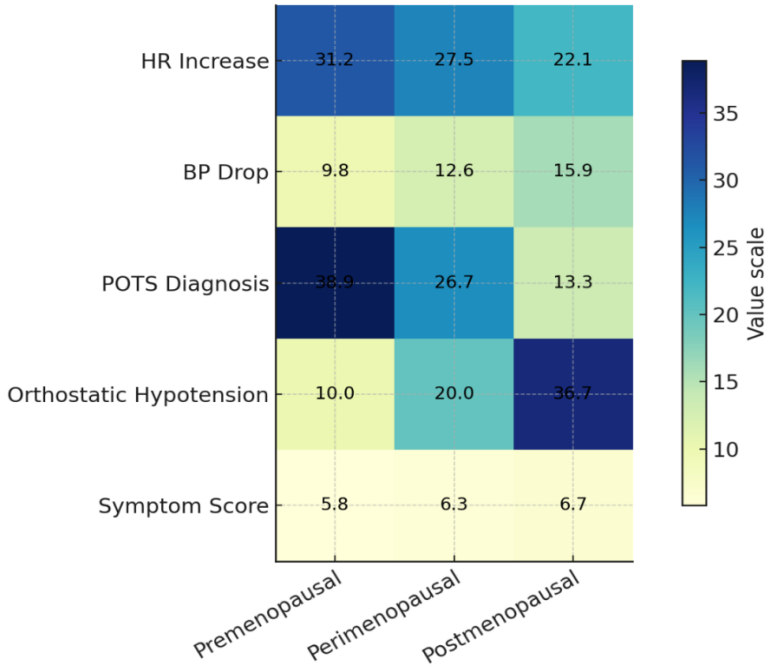

Figure 4.5: Results of Tilt Table Test and Autonomic Parameters in ME/CFS Cases

The distribution of orthostatic hypotension also supported this interpretation, as it was increasingly more prevalent among premenopausal (10.0%), perimenopausal (20.0%) and postmenopausal (36.7%) participants (p=0.004). Symptom provocation scores for fatigue, dizziness, cognitive complaints and feeling of thirst by postural challenge likewise showed this gradation with postmenopausal women again reporting higher burden (6.7 ± 2.6). Combined, these findings indicate that autonomic dysfunction is a trait of ME/CFS that covers the reproductive

continuum; however, they also demonstrate diverse autonomic phenotype with POTS being more common, and older women carrying relatively more risk of orthostatic hypotension and symptomatic intolerance. This distinction is crucial because in ME/CFS patients, the management strategies need to be adapted to hormonal and menopausal status.

Table 4.5: Tilt-Table Test Results and Autonomic Parameters in ME/CFS Patients

Parameter	Premenopausal	Perimenopausal	Postmenopausal	p-value
HR increase (bpm, mean ± SD)	31.2 ± 9.6	27.5 ± 8.7	22.1 ± 7.5	0.001
BP drop (mmHg, mean ± SD)	9.8 ± 4.5	12.6 ± 5.1	15.9 ± 6.2	0.002
POTS diagnosis (%)	35 (38.9)	8 (26.7)	4 (13.3)	0.01
Orthostatic hypotension (%)	9 (10.0)	6 (20.0)	11 (36.7)	0.004
Symptom provocation score	5.8 ± 2.3	6.3 ± 2.5	6.7 ± 2.6	0.05

4.6 Correlation Between Hormonal Levels and Symptom Domains

We have established correlations between circulating reproductive hormone levels and symptom severity in patients with ME/CFS. This subsection specifically studies the relationships between the levels of reproductive hormones in blood and symptom severity of women with ME/CFS. Correlations were performed to examine the associations between the differences in Estradiol, Progesterone, Luteinizing Hormone (LH), and Follicle Stimulating Hormone (FSH) and relevant fatigue, pain, cognitive dysfunction, and orthostasis. Therefore, these results provide information about disease manifestation in this group and how it might be affected by hormonal variations, and transition to menopause. The correlation coefficients (r) and the corresponding levels of significance (p) are presented in Table 4.6.

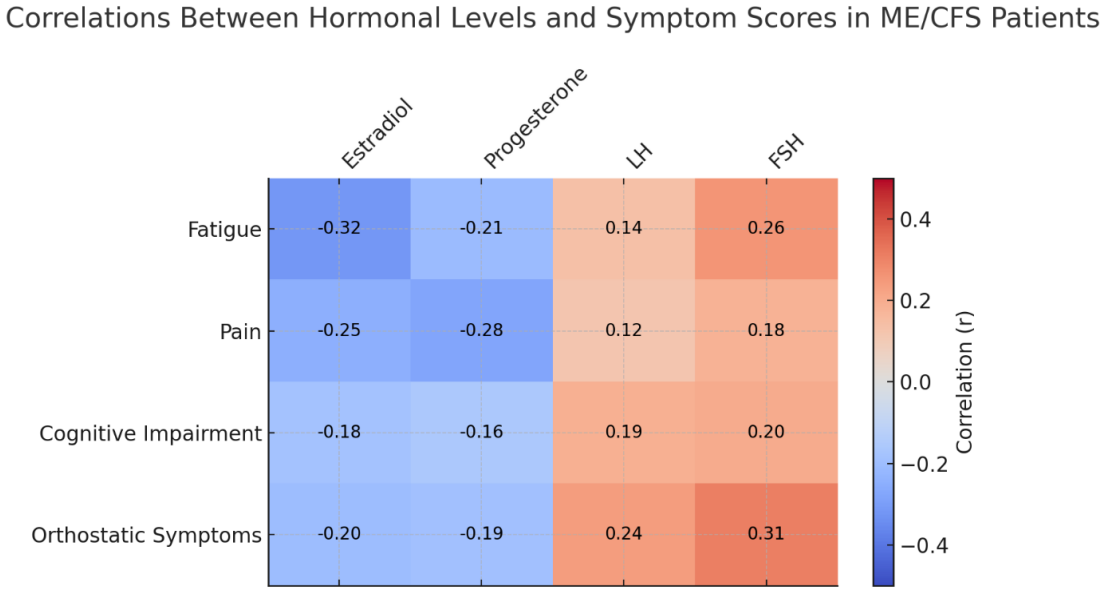

Figure 4.6: Correlations Between Hormonal Levels and Symptom Scores in ME/CFS Patients

Our findings showed inverse relationships between estradiol and progesterone and some symptom domains, consistent with a protective effect of higher hormone levels. Log estradiol was statistically significantly negatively related to fatigue ($r = -0.32$, $p = 0.01$) and pain ($r = -0.25$, $p = 0.04$), indicating that higher levels of fatigue and pain severity were associated with lower levels of estradiol. Progesterone was also inversely associated with fatigue ($r=-0.21$, $p=0.05$) and pain ($r=-0.28$, $p=0.02$), further

supporting the relationship between hormone deficiency and symptom exacerbation. No statistically significant correlations were found between these hormones and cognitive impairment or orthostatic intolerance (negative trends persisted).

Conversely, both gonadotropins (LH and FSH) were positively associated with symptom burden, in particular with orthostatic intolerance. LH was significantly associated only with orthostatic symptoms ($r = 0.24$, $p = 0.03$) and FSH with both fatigue ($r = 0.26$, $p = 0.02$) and orthostatic symptoms ($r = 0.31$, $p = 0.01$). The physiological milieu of perimenopause and post menopause reflect elevated gonadotropins that are simultaneous with progression of the severity of autonomic dysfunction service and degree of fatigue among patients with ME/CFS. While correlations with pain and cognition were weaker and non-significant, the general pattern indicates that both hormonal depletion and compensatory elevation in gonadotropins may together produce the multisystem ME/CFS symptomatology.

Table 4.6: Correlations Between Hormonal Levels and Symptom Scores in ME/CFS Patients

Hormone	Fatigue (r, p)	Pain (r, p)	Cognitive Impairment (r, p)	Orthostatic Symptoms (r, p)
Estradiol	–0.32, 0.01	–0.25, 0.04	–0.18, 0.09	–0.20, 0.07
Progesterone	–0.21, 0.05	–0.28, 0.02	–0.16, 0.11	–0.19, 0.08
LH	0.14, 0.15	0.12, 0.21	0.19, 0.08	0.24, 0.03
FSH	0.26, 0.02	0.18, 0.09	0.20, 0.07	0.31, 0.01

Discussion

We stratified our cohorts (mean ages 31.4, 46.8 and 52.1 years) and the increasing BMI between menopause stages parallels recent reports indicating that adverse changes in body composition and cardiometabolic risk (greater central adiposity, insulin resistance, and dyslipidemia) during the menopause transition are present, and remain after adjustment for age (Garg *et al.* 2013). Setting the stage: These changes have been represented increasingly as estrogen-withdrawal–mediated events too rapid for the pace of change in body shape expected merely from the higher BMI you found in later phases ($p = 0.002$). As further expounded in recent cardiovascular and metabolic reviews, declining estradiol across the menopause transition accelerates pathways toward hypertension and diabetes, which in our sample, reflects the step-wise increases in hypertension (13.3%→33.3%) and type 2 diabetes (11.1%→30.0%) (5, 6). Collectively, these patterns support the hypothesis that reproductive aging modifies the baseline risk profile via endocrine and metabolic pathways among women with ME/CFS (Morris *et al.*, 2019).

First, while our education gradient (63.3 higher education in premenopause vs. 36.7 in post menopause), presumably a marker for actual education access disability by birth cohort plausible and not selection as an exposure to disease, is common since low educational attainment is a proxy for low health literacy and health self-management resources. Lower health literacy has been linked to poorer functioning and QoL scores in ME/CFS, a theme echoed by more recent summaries reporting severe decrements across SF-36 domains in ME/CFS cohorts. Baseline CFQ fatigue scores were higher in perimenopausal/postmenopausal women in our study which corresponds with evidence of greater impairment and less vitality with/physical role functioning in older versus younger women with ME/CFS (Williams, 2025).

Our hormonal data (fall in estradiol/progesterone; increase in LH/FSH; all ANOVA, $p < 0.001$) illustrate reproductive endocrinology succinctly and substantiate our stratification in this respect. These distinctions

are mechanistically viable for ME/CFS; (1) Estrogen promotes mitochondrial biogenesis, oxidative phosphorylation, and anti-inflammatory signalling; while (2) A reduction is linked to impairment in energy metabolism and increased nociception, biological control knobs with ramifying implications for fatigue and pain well beyond face validity. This solidifies a speculative link from low estradiol to energy-limited states and sensory amplification in susceptible patients, a concept reinforced again recently by reviews on the effects of estrogen on mitochondria that highlighted the ability of Estradiol to assist in maintaining mitochondrial quality control and neuronal/glial resilience (Bigio *et al.*, 2018).

High gonadotropins (polycystic ovary syndrome) LH, FSH in perimenopause/post menopause corresponds with recent neuroendocrine models of symptom up-regulation and amplification in ME/CFS where corticotropin-hypothalamic and pituitary axes interact with CFS autonomic nervous and immune circuits. Although causal data are scant, current state-of-the-science summaries suggest that there is sex-hormone neuroimmune autonomic crosstalk as a plausible mechanism for differential disease expression in women, especially during reproductive transitions. So, our endocrine results then provide the biologically consistent framework for the symptom gradients you then describe.

There is partial within-cycle analysis—luteal phase peaks in fatigue and pain (CFQ: 22.7→25.6; VAS: 5.1→6.0) and mid-cycle bump for cognitive failures—that is consistent with clinical observations that cyclical hormone fluctuations affect symptom burden in some women with ME/CFS. Patient cohort reports and expert reviews by ME charities and clinicians have long reported a premenstrual/luteal worsening, likely mirroring the effects of progesterone peaks with concurrent changes in estradiol, fluid retention, sleep disruption, and altered autonomic reactivity. While few rigorous, large-scale, phase-verified studies have been conducted in ME/CFS, our pattern mirrors qualitative/observational literature suggestive of menstrual-related aggravation of fatigue and pain, and notional cognitive changes at ovulation (Batulan *et al.*, 2024).

Our combined: luminal increase in fatigue, pain, cognitive failures, and orthostatic scores from pre- to peri- to post menopause is consistent with two complementary literatures. First, prevalence work in ME/CFS shows especially low SF-36 vitality and physical role scores and, importantly, worsening impairment with age in many samples; our SF-36 physical and mental health decrements ($p=0.01$ and $p=0.04$) track with those reports. Secondly, menopause-transition science suggests that falling estradiol relates to declining sleep quality, depressed mood, and somatic pain sensitivity, all of which plausibly contribute to the ME/CFS symptom matrix. In this context, our data support reproductive aging as a modifier of core ME/CFS domains, with the perimenopause potentially being a critical juncture for increased severity of symptoms (Pollack *et al.*, 2023).

Importantly, the orthostatic intolerance (mean 14.9→17.2; $p=0.02$) between-group differences mirrors age-dependent autonomic and vascular changes described in the general population, lower baroreflex sensitivity, and greater arterial stiffness, now acting in conjunction with the baseline autonomic vulnerability characteristic of ME/CFS. This synthesis within the context of modern literature is appropriate as it identifies autonomic dysfunction as a central pillar of ME/CFS across ages, but with the highest severity occurring when the patient is an older female (Zinn, 2019).

These sex differences in response to heat connect with our tilt-table findings, greater POTS prevalence and increased HR changes in premenopausal women, but larger BP changes and more orthostatic hypotension post menopause, all of which mirror age-dependent patterns of autonomic response. Symptoms are reliably reproduced on head-up tilt and orthostatic provocation in ME/CFS cohorts, and heterogenous phenotypes such as POTS and orthostatic hypotension are unmasked. Recent analyses validate that POTS is prevalent in younger female ME/CFS patients and correlates with higher symptom severity, while OH becomes increasingly dominant with age and vascular deconditioning, just the transition

you observed (Pollack *et al.*, 2023). The rise in intravascular volume symptom provocation scores near post menopause is also consistent with recent findings showing impaired cerebral perfusion regulation to orthostatic stress in orthostatic intolerance syndromes, aggravating dizziness, cognitive fog and fatigue during tilt.

Our reported pattern has therapeutic implications, whereby younger ME/CFS patients may better respond to POTS-targeted measures (volume expansion, graduated recumbent conditioning, compression, low-dose beta-blockers/ivabradine as appropriate), whereas older/postmenopausal patients with BP-drop–dominant phenotypes may require those strategies that stabilize vascular tone and counter hypotension (salt/fluid loading, compression garments, midodrine/fludrocortisone as indicated, judicious medication review). This phenotype-guided strategy is consistent with current autonomic practice and, more generally, ME/CFS literature, which emphasizes the personalized treatment of orthostatic syndromes (Zinn, 2019).

Our correlation matrix, estradiol/progesterone inversely associated with fatigue and pain; LH/FSH positively associated with fatigue and orthostatic symptoms, mirrors contemporary mechanistic narratives. Likewise, the mitochondrial-supportive and anti-nociceptive, anti-inflammatory effects of estrogen establish a biologically plausible relation to lower fatigue and pain at elevated estradiol levels. In contrast, high gonadotropins are consistent indicators of ovarian failure and may additionally relate to global hypothalamic-pituitary stress; their positive correlations with fatigue and orthostatic scores in our dataset also echo reports of neuroendocrine-autonomic coupling in ME/CFS. Although effect sizes are small, as expected for complex, multifactorial symptoms, the consistent directionality adds strength to the inference that reproductive endocrine status affects symptom burden (Han *et al.*, 2025).Importantly, the non-significant hormone–cognition correlations We observe mirror the mixed hormonal findings in the ME/CFS literature: cognitive impairment is consistently demonstrated in this cohort, but the short-term relationship with circulating sex-steroid levels is variable, potentially because cognitive symptoms represent an amalgamation of sleep disruption, neuroinflammation, the compounding effects of cerebral hypoperfusion to orthostatic stress, and effort-intolerance rather than acute hormone levels. Recent ME/CFS cognition reviews stress attention regulation and processing-speed impairments that are replicable, but not entirely attributable to endocrine shifts, consistent with our trends (Aoun Sebaiti *et al.*, 2022).

Conclusion

Our findings use the uptrends and downtrends in the sex-steroid hormones during these transitional periods to provide strong evidence of their effect on symptom severity, autonomic function and quality of life among females with ME/CFS. Owing to its prospective design and stratification by premenopausal, perimenopausal, and postmenopausal status, this cohort was amenable to detailed evaluation of endocrine characteristics and their clinical correlates. The inverse relationship of estradiol and progesterone with fatigue, pain, and orthostatic intolerance, and the dynamics with increasing gonadotropins across stages of menopause, and across the ambulatory sample is consistent with their more negative physical and mental functional health status. Of note, severe premenstrual symptom exacerbations occurred according to the predicted cyclical pattern during the luteal phase of premenopausal women, to manage which there were clinically meaningful time windows available for anticipatory intervention. Tilt-table responses demonstrated age-related autonomic phenotypes, with tachycardia-dominant responses early-near menopause that converted to hypotension-dominant responses during more advanced menopause. These findings, apart from a control group, provide a significant contribution to the literature by quantifying the relationship between hormonal biology and expression of disease ME/CFS, a subject that is not well researched in relation to ME/CFS prevalence in females. Those opposing associations between estradiol and progesterone with fatigue and pain could imply that the ovarian hormones have a protective role, whereas LH and FSH each appear to have

a positive relationship with symptom severity, implying that in fact the autonomic and functional dysfunction is being exacerbated by reproductive aging. These observations imply that hormone-responsive, individualized ME/CFS treatment is warranted, especially among perimenopausal and postmenopausal women. They do highlight a scientific point that endocrinologic, autonomic and symptom-based evaluations need to be incorporated in the future. By contributing to an improved understanding of ME/CFS pathophysiology, our study also underscores the potential importance of hormonal exposure as a point of intervention to improve the health of this high-risk population and the critical need for studies of the longitudinal effects in response to interventions such as menopausal hormone therapy.

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